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Navigating a Two-Way Street: Metal Toxicity and the Human Gut Microbiome

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For populations worldwide, exposures to arsenic (As) and mercury (Hg) are a fact of life.[1,2] Millions of people consume drinking water with elevated As levels, potentially increasing their risk of cancer and other diseases[3]; as for Hg, billions regularly consume seafood[4] or rice,[5] the most common exposure sources. These widespread exposures and their potentially severe adverse health effects make As and Hg sources of concern across the globe.

Both As (a metalloid that combines properties of metals and nonmetals[6]) and Hg exist in elemental, organic, and inorganic forms.[7,8] Most research on health effects has focused on inorganic arsenic (iAs) and the organic compound methylmercury (MeHg); organic As (oAs) and inorganic Hg (iHg) are thought to be less toxic.[8,9,10,11,12] Many studies have demonstrated the toxicity of iAs and MeHg; however, not everyone responds to exposures in the same way.

Recently, researchers have homed in on the role of the human microbiome in mediating how As and Hg affect chronic disease risk.[2,13] Their work is revealing complex and bidirectional interactions between these toxic metals and the trillions of microbes in our gut.[2]

Arsenic Sources and Toxicity

Natural weathering and erosion cause certain minerals in rocks to release iAs into the soil, where it dissolves into groundwater and surface water. Although geology is the cause of most As contamination in drinking water, human activities—such as coal burning, mining, and smelting—can also contribute.[7]

Drinking water is the most common source of human exposure to iAs.[3] Some 200 million people worldwide—in Bangladesh, India, Argentina, the United States, and elsewhere—regularly drink water with iAs concentrations exceeding the World Health Organization guideline of 10 μg/L.[3,14] Infants are at particular risk when formula is mixed with iAs-contaminated water.[15]

Rice and seafood are also significant sources of As exposure.[5,10] Rice is a staple food for 3.5 billion people,[5] and fish is an important source of animal protein for more than 3 billion people.[4] Rice, which is typically grown in flooded paddies,[16] is what is known as a hyperaccumulator; the plants readily take up iAs from the soil or irrigation water.[17] The metal then concentrates in the outer layer of the grain.[18]

Seafood, especially shellfish, is known to contain organic arsenicals.[10] Although generally considered less toxic than iAs, some oAs compounds and metabolites have demonstrated cytotoxic effects *in vitro*.[19,20,21] Margaret Karagas, a professor of epidemiology at the Dartmouth Geisel School of Medicine, believes more detailed studies are needed on the prevalence and toxicity of oAs compounds in both seafood[10] and rice.[22] "In parts of the world where arsenic levels in drinking water are not elevated, food is the main exposure source, especially for babies and children who regularly consume rice cereal or rice," says Karagas. "Relative to body weight, arsenic levels in young children can be three times higher than in adults."[23]

iAs is a Group 1 carcinogen causally linked to skin, bladder, and lung cancer, with probable or possible links to several other

Most arsenic contamination results from natural sources, whereas most mercury contamination comes from human activities. Images, left to right: © HM Shahidul Islam/Shutterstock; © iStockphoto/6381380.

cancers.[24] It has also been associated with type 2 diabetes and diseases of the cardiovascular, nervous, respiratory, and immune systems.[3] iAs and its metabolites can cross the placenta,[25] and fetal exposure has been associated with lower birth weight[26] and adverse neurodevelopmental effects.[27,28,29]

Mercury Sources and Toxicity

In contrast to As, the majority of Hg contamination occurs as a result of human activities, especially fossil fuel combustion.[30] Hg emissions can travel far from the original source before being deposited, on soil and water. Aquatic bacteria convert deposited Hg to MeHg, which marine creatures readily absorb. MeHg biomagnifies from the bottom to the top of the marine and freshwater food webs[30]; levels in the tissue of predatory ocean fish and mammals can be more than a million times higher than in the surrounding water.[31] This means that populations with high seafood consumption rates, such as coastal Indigenous peoples with strong cultural ties to the sea[4,32] may experience chronic high exposures to MeHg.

Bacteria in flooded rice paddies produce MeHg that can reach the grain.[16] Although rice typically contains a lower proportion of MeHg than seafood, exposure levels can be substantial in populations that consume rice several times a day.[33] As with iAs, this exposure is a concern for infants who regularly eat rice cereal and other rice-derived foods.[1] Some studies suggest that the consumption of several daily rice meals during pregnancy may be more harmful to the fetus than a MeHg-rich seafood diet, which offers nutritional benefits that somewhat offset the compound's toxicity.[34,35]

Large-scale exposure events led to a strong research focus on the neurotoxicity of MeHg,[36] which readily crosses the placenta and blood–brain barrier.[37] MeHg biomagnifies from mother to fetus,[38,39] so neurological damage from high exposure during pregnancy is typically greater in the fetus than in the mother.[38,39]

Beyond its neurotoxic effects, MeHg has been associated with cardiovascular[40,41,42,43,44] and immune system[45] disorders. Potential cancer links have also been reported[46] but are much less established than for iAs. In a study of young children, Karagas et al. reported associations between early-life Hg exposures (as estimated by toenail and urine samples) and increased blood pressure, which is an important risk factor for hypertension in adulthood.[44] "Capturing these [exposure-related] changes early gives us the opportunity to intervene and positively impact lifelong health," says Karagas.

In still another associated outcome, Matthew Rand, an associate professor of environmental medicine at the University of Rochester, studies the role of MeHg in skeletal muscle disorders.[47] "These conditions have traditionally been attributed to central nervous system disruptions," says Rand. "But skeletal muscle abnormalities may also cause motor symptoms, which has been explored much less."

Metabolism by Human and Microbial Enzymes

The human gut microbiome plays a substantial role in the metabolism—and hence toxicity—of iAs.[48] This may also be true for MeHg, but the exact process is largely unknown.[49]

The human enzyme AS3MT metabolizes iAs via methylation in the liver[50]—a complex, multistep process. Of the intermediate organic arsenicals generated in that process, some are more and others less toxic than iAs.[51] After passing through the kidneys, about 90% of ingested iAs eventually leaves the body in urine and less than 10% in feces, although this varies across species and may depend on whether exposure comes from water or food.[52,53,54] The liver also releases some arsenicals into bile, which flows into the small intestine to help digest dietary fats.[55] Arsenicals may accumulate in tissues, particularly the kidneys.[56]

Although it has long been known that microbes in the human gut also methylate iAs,[57] researchers are still exploring the relative roles of human and microbial genes. A study led by Seth Walk, an associate professor of microbiology and cell biology at Montana State University, found that a healthy human microbiome transferred into germ-free *As3mt* knockout mice via fecal transplant completely protected the mice against the lethal effects of acute iAs exposure.[48] This was partially due to the activity of the arsenic methyltransferase (*ArsM*) gene cluster[58]—the bacterial analog of the human *AS3MT* gene—in the common gut microbe *Faecalibacterium prausnitzii*.[48]

Walk's report[48] revealed a surprisingly large collective role of gut microbes in host toxicity. In a follow-up study, his group transferred *Escherichia coli* bacteria into the gut of germ-free mice so that the mouse microbiome contained only these bacteria. Some mice received *E. coli* that had been genetically manipulated to produce a specific arsenic-binding protein. These animals excreted significantly more arsenic in stool than controls without the protein, resulting in less organ accumulation. The study showed that this single microbial protein was sufficient to protect the mice against the lethal effects of arsenic.[59]

Ingested MeHg is absorbed by the blood and carried to target tissues, including the brain and the developing fetus. Most MeHg is excreted from the liver into bile and enters the enterohepatic (intestine–liver) cycle. This cycle promotes the biomagnification of MeHg because it allows the metal to reenter systemic circulation.[60] Up to 95% of ingested MeHg is eventually excreted in the feces and the remainder in the urine as iHg. MeHg leaves the body much more slowly than iAs, at an approximate rate of 1.4% per day.[60]

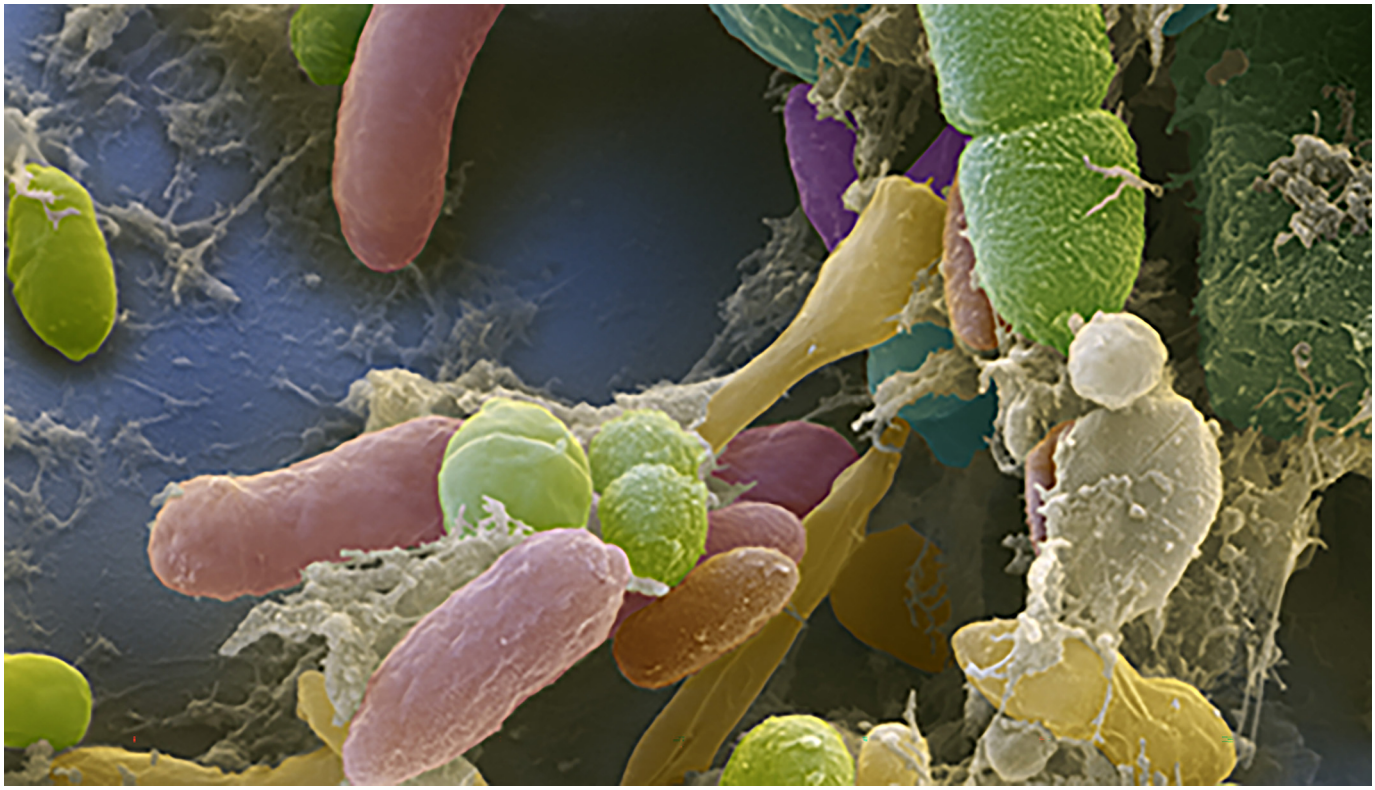
Elimination of MeHg from the body requires demethylation, but the chemical bond between carbon and mercury is difficult to break.[61] Researchers reported in the 1970s that rodents depleted of their gut microbes had reduced excretion rates and increased tissue retention times of MeHg in the brain and other organs.[62,63,64] This suggests that specific gut microbes may perform the demethylation reaction and could reduce human toxicity.[48] However, underlying mechanisms and microbial species have not yet been identified.[60]

"The bacterial *Mer* [gene cluster] is a well-known enzymatic demethylation system, but there is little evidence that it is present in the human gut," says Rand. "Demethylation in the gut lumen may involve a consortium of bacteria or an abiotic rather than enzymatic process." Abiotic processes in living cells may be driven by physical conditions such as temperature, pH, water, or oxygen levels.[65]

Variations in Toxicity

The typical half-life in the human body is 4 days for iAs[66,67] and 50 days for MeHg,[60] but people with similar exposure levels metabolize the metals at variable rates. This is especially true for MeHg, where reported half-lives range from less than 30 to more than 120 days.[60] The reasons for this variation include physiological, genetic, and microbial factors.

Sex, age, and muscle mass are physiological influences on toxicity. For example, in humans and other species, females may methylate iAs more efficiently than males.[50] For MeHg, Rand's group developed computational pharmacokinetic models that predicted a shorter MeHg half-life in women than men and a shorter half-life in children than adults.[49] The models also identified skeletal muscle mass as a potential storage compartment that can delay the fecal excretion of MeHg.[49] Because both iAs and MeHg are transported across the gut epithelium into the bloodstream and



This color-enhanced scanning electron micrograph shows different bacteria from a human fecal sample. Magnification 5,000× (at 10-cm wide image size). The trillions of microbes in our gut have a dynamic relationship with environmental agents and may play a role in determining why some people experience worse effects than others from the same exposure level. Image: © Eye of Science/Science Source.

from the liver into the blood or bile, any host or microbial effects on transport efficiency, gut barrier function, and tissue absorption rates also modulate metabolism and body burden.[54,68,69,70,71]

AS3MT is the major genetic factor that influences iAs metabolism; multiple other genes[72] and epigenetic factors[73] make smaller contributions. The evolutionary importance of *AS3MT* is supported by studies led by Karin Broberg, a professor of environmental medicine at the Karolinska Institute and Lund University, Sweden. She identified a positive *AS3MT* selection signature in the genome of an Indigenous population in the Andes Mountains of Argentina.[74] These people have consumed drinking water with high iAs concentrations for thousands of years. The absence of typical arsenic-related health effects and much higher frequencies of several *AS3MT* variants, compared with genetically similar communities without high iAs exposures, suggest that this population has developed iAs resistance via natural selection.[74]

A higher frequency of ArsM-carrying gut microbes may also contribute, suggests Broberg, but that hypothesis has not been studied yet. The geologic contamination of drinking water has existed for a very long time, whereas human-caused increases in atmospheric Hg are more recent. This difference, says Broberg, may explain the evolution of the *AS3MT* defense system in many species[58,75,76] and the lack of an analogous MeHg system. "I find it very interesting that the same arsenic defense system exists in bacteria and humans because this is not the case for many other environmental chemicals," she says.

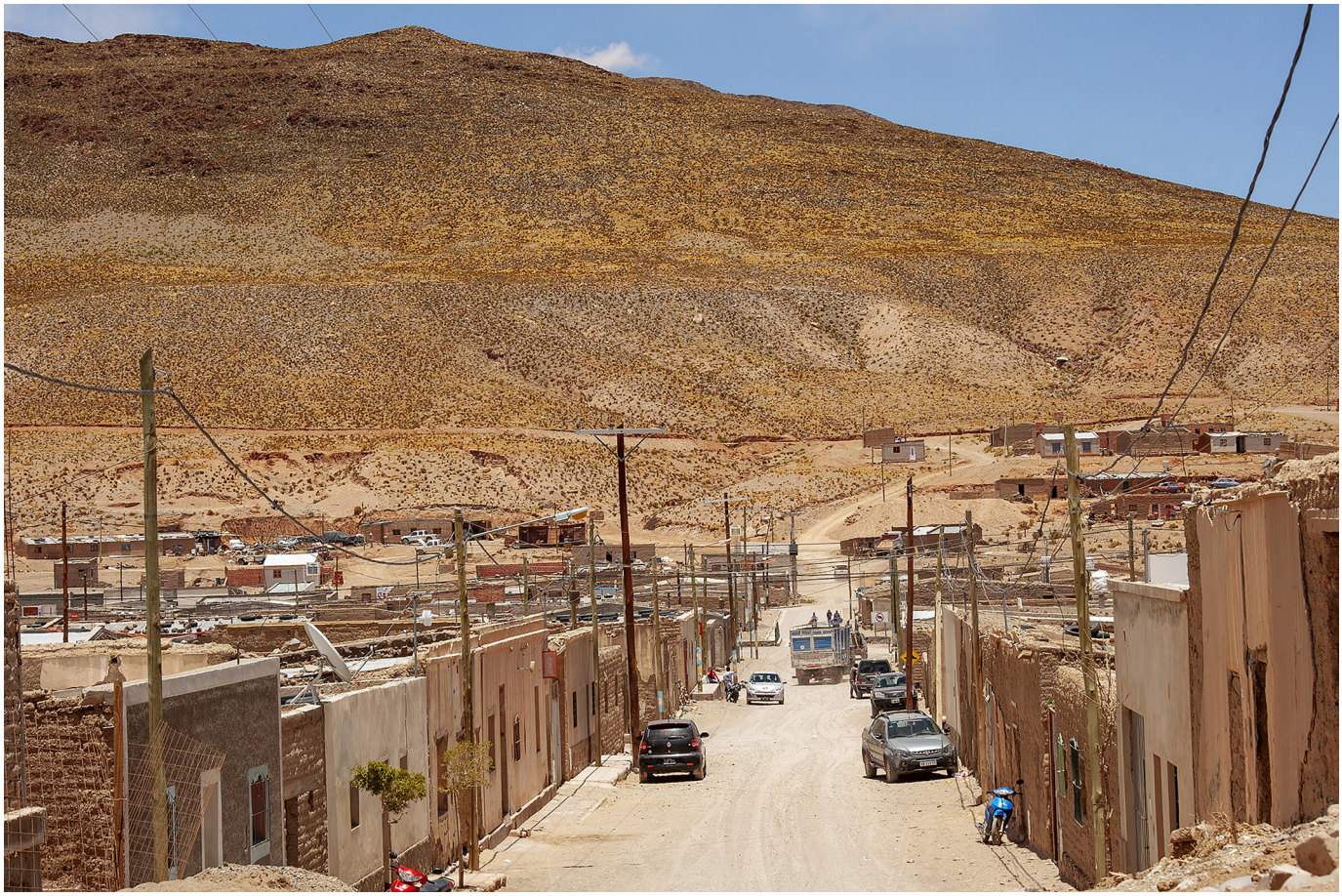
Exposure and Microbial Diversity

Microbial influences on human toxicity go beyond the direct metabolism of iAs. Because both metals have historically been used as antimicrobial agents,[77,78] it is plausible that they may reduce the diversity of microbes in the gut. "This is especially worrisome for infants and young children," says Juliette Madan, a neonatal perinatologist and professor of epidemiology at the Dartmouth Geisel School of Medicine. "[Exposure to metals may change] the developmental trajectory of their gut microbiome during a critical period when their immune system is being trained and their body is learning to metabolize food."

Analyzing data from the New Hampshire Birth Cohort Study, Madan and Karagas found that higher urine As concentrations in babies were associated with a reduced frequency in stool of multiple microbial genera involved in immune system development.[79] A later analysis, which used toenail clippings to assess exposure to a variety of trace elements, associated higher As levels with reduced gut microbial diversity in all the infants. The same association was observed with higher Hg levels in a subset of babies.[80] Higher MeHg concentrations in stool were also associated with lower microbial diversity in a small study of pregnant women.[81]

Curtis Huttenhower, a professor of computational biology and bioinformatics at the Harvard T.H. Chan School of Public Health, notes that studies of exposure effects on microbial diversity require special care because chronic health conditions, the therapeutics used to treat them, and many dietary and environmental exposures all affect microbiome composition in similar ways. This means that quality control methods for laboratory and statistical analyses of microbiome samples are critical to avoid spurious associations.[82,83]

The known microbial influences on the human toxicity of iAs and MeHg may only be the tip of the iceberg.[84,85] In natural environments, for example, the As defense systems of soil and aquatic bacteria regulate an exceptionally wide range of cellular processes beyond iAs methylation, including sugar transport,



For millennia, populations in the Andean highlands have consumed water with naturally high concentrations of arsenic. Studies in towns such as San Antonio de Los Cobres, Argentina (shown), indicate that the people here have evolved resistance to arsenic toxicity. Image: © iStockphoto/FernandoQuevedo.

copper tolerance, and iron homeostasis.[84] Walk says this fact—along with recent rodent findings[86]—suggests that microbes in the human gut may transform iAs in additional ways that indirectly influence toxicity, perhaps by producing arsenicals that more easily cross cell membranes. "We think the total microbial influence on arsenic biochemistry is larger than the host's and likely involves many different types of biotransformation," adds Walk. "Methylation is just one of these."

Similarly, says Sarah Rothenberg, an associate professor of environmental health at Oregon State University, microbial influences on MeHg toxicity may not be restricted to demethylation. "It is quite possible that gut microbes may help regulate neurotransmitters through the gut–brain axis, as some studies[87,88] have suggested," she explains. In other words, the microbiome may contribute to the notorious neurotoxic effects of MeHg through a variety of mechanisms. Further study could clarify the full range of bidirectional interactions between iAs, MeHg, and the gut microbiome.

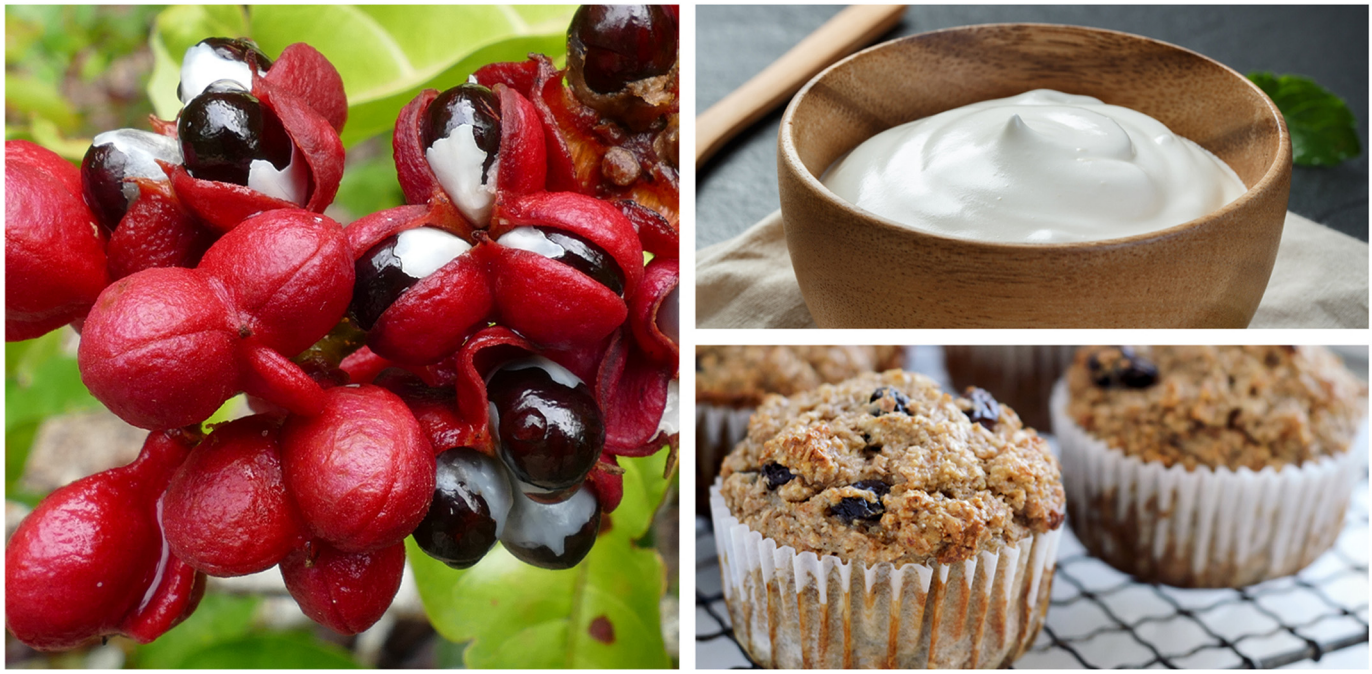
Exploring Structural and Dietary Interventions

Human exposure to As and Hg can be reduced by treatment and regulatory actions. For example, arsenic removal plants have greatly improved the quality of drinking water quality in parts of Chile,[89] and researchers elsewhere are exploring new ways of treating drinking water at the community and household levels.[90,91] National policies and international agreements have helped reduce mercury emissions from power plants.[92,93] Rothenberg has shown that certain water management strategies for rice paddies can substantially reduce MeHg levels in rice[94]; similar reductions may be possible for organic arsenicals.[95] Breastfeeding can help protect babies from exposure to iAs in both powdered infant formula and drinking water,[96] although breast milk can carry MeHg.[97]

When exposures are impossible to avoid, emerging evidence for microbial influences on metal toxicity supports dietary supplements as potential interventions. This strategy holds promise because the microbiome is known to be dynamic[98] and modifiable.[99] For example, eating yogurt enriched with *Lactobacillus rhamnosus* was associated with lower blood concentrations of As and Hg in pregnant women in a small pilot study in Tanzania.[100] In larger trials, folic acid supplements were associated with more efficient iAs metabolism in folate-deficient Bangladeshi adults with high exposure.[101,102]

Promoting the growth of ArsM-carrying species such as *F. prausnitzii*, which has already been studied as a probiotic,[103,104] may be another strategy. Environmental microbes are capable of removing iAs from water through bioaccumulation,[105,106] so future research could explore multiple mechanisms for detoxifying iAs, including methylation and accumulation within gut microbes.[48]

Because none of the bacterial species that demethylate MeHg in the environment[107] have been found in human stool, dietary supplements that would reduce the compound's toxicity are more challenging to design.[108] Wheat bran and other grains,[109,110] fruits,[110,111] compounds in plants,[112] and dietary supplements[113] may accelerate the excretion of MeHg as inorganic Hg, and microbial contributions to some of these processes are plausible.



Human and animal studies suggest that consumption of certain foods—such as guarana fruit (left), *Lactobacillus*-rich yogurt (top right), and wheat bran (bottom right)—may be one way to metabolize iAs and MeHg more efficiently. In some studies, this action was shown to occur through interaction with the gut microbiome. Images, clockwise from left: © juerginho/adobe.stock.com; ©DN6/adobe.stock.com; © LIF2/Shutterstock.com.

For example, a fiber-rich diet of wheat bran reduced the half-life of MeHg in mice by more than 40%—most likely, the authors speculated, due to increased demethylation by gut microbiota.[109]

These types of studies generally support the feasibility of precision nutrition—making dietary recommendations based on an individual's genetic makeup, health history, lifestyle, environmental exposures, and microbiome composition.[114] "Modifying the microbiome therapeutically for a specific purpose—like promoting iAs methylation or MeHg demethylation—is easier to do early in life when the microbial community is not yet fully established," says Huttenhower. "Later in life, it will require bigger perturbations, such as fecal transplants." That procedure, he adds, already works very well in patients with *Clostridium difficile* infections and inflammatory bowel disease.

Madan agrees with the importance of early interventions. She particularly encourages the promotion of breastfeeding as one way to reduce iAs exposure and shape a healthy microbiome.[115] (In some communities, however, this may require providing resources and support for nursing women.[116]) Testing the effectiveness of probiotic supplements is another promising strategy because, she says, "diet is how we change lives, especially in high-risk populations."

Walk is encouraged by the wide range of biotransformations performed by environmental microbes. Establishing microbes in the human gut to perform a specific function, he says, may be a feasible alternative when exposures cannot be avoided. This, he believes, "will drive the next phase of developing probiotics and microbiome-focused therapies."

Silke Schmidt, PhD, writes about science, health, and the environment from Madison, Wisconsin.

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